ANTIBODIES, AND BISPECIFIC ANTIGEN-BINDING MOLECULES THAT BIND HER2 AND/OR APLP2, CONJUGATES, AND USES THEREOF

FIELD OF THE INVENTION

[0001] The present invention relates to antibodies, and antigen-binding fragments thereof, which are specific for human epidermal growth factor receptor 2 (HER2), and methods of use thereof. The present invention also relates to bispecific antigen-binding molecules that bind HER2 and amyloid precursor-like protein 2 (APLP2), and methods of use thereof. The present invention further relates to antibody-drug conjugates comprising an anti-HER2 antibody, or anti-HER2/anti-APLP2 bispecific antibody, or fragment thereof and a therapeutic agent (e.g., a cytotoxic drug).

BACKGROUND

[0002] Human epidermal growth factor receptor 2 (HER2) is a tyrosine kinase receptor growth-promoting protein found on the surface of some cancer cells and is associated with aggressive disease. About one in five breast cancers overexpress HER2. To be considered HER2-positive, tumor cells are usually tested by one of two methods: immunohistochemistry (IHC) or fluorescent in situ hybridization (FISH). IHC test results are reported as: 0, IHC1+, IHC2+ or IHC3+. A finding of IHC3+ is considered HER2-positive. A finding of IHC2+ is borderline and typically is confirmed by a positive FISH test.

[0003] HER2 is a clinically validated antibody-drug conjugate (ADC) target in breast cancer. To achieve maximal anti-tumor effect, the ADC must bind specifically to HER2 and internalize into the cell, where ADC processing results in release of the toxin into the cytosol. While a high degree of tumor specificity and surface expression levels are known to be essential features of a good ADC target, the trafficking properties of ADC targets have not been thoroughly explored.

[0004] For example, a HER2 targeting antibody conjugated to the potent toxin maytansine "DM1" (Trastuzumab-emtansine, or T-DM1) is approved for the treatment of metastatic breast cancer. However, inefficient lysosomal trafficking of HER2 limits T-DM1 efficacy to those patients that express very high levels of HER2 (IHC 3+, or FISH amplification ratio >2). Significant efforts are being directed towards generation of HER2-ADCs that efficiently induce regression of tumors expressing intermediate HER2 levels (IHC2+). These efforts rely on the use of more potent toxins and/or on enhancing HER2 internalization.

[0005] APLP2 is a single pass transmembrane protein (Uniprot Q06481) with tyrosine-based internalization signals. Multiple APLP2 isoforms have been reported (Li, C., et al. *Cancer Res.* 2006 Feb. 15; 66(4):1990-9; Pandey, P., et al. *Oncotarget.* 2016 Apr. 12; 7(15):19430-44. doi: 10.18632/oncotarget.7103). APLP2 is ubiquitously expressed in normal tissues and reported to be overexpressed in certain cancers (Pandey, P., et al. *Oncotarget.* 2015 Feb. 10; 6(4):2064-75.). Consistent with its subcellular localization in intracellular vesicles, APLP2 is efficiently internalized from the plasma membrane and targeted for rapid lysosomal degradation. A suggested biological function of APLP2 is to promote lysosomal targeting and degradation of PCSK9 and MHC class I (DeVray, R. M., et al. *J Biol Chem.* 2013 Apr. 12; 288(15):10805-18. doi: 10.1074/jbc.M113.453373. Epub 2013 Feb. 19.; Tuli, A., et al. *J Biol Chem.* 2009 Dec. 4; 284(49):34296-307. doi: 10.1074/jbc.M109.039727. Epub 2009 Oct. 6).

[0006] Antigen-binding molecules that enhance HER2 internalization and/or trafficking to lysosomes would provide useful therapies where specific targeting and killing of HER2-expressing cells is desired.

BRIEF SUMMARY OF THE INVENTION

[0007] In a first aspect, the present invention provides bispecific antibodies and antigen-binding fragments thereof that bind human HER2 and human APLP2. The bispecific antibodies according to this aspect of the invention are useful, inter alia, for targeting cells, e.g., breast cancer cells, expressing HER2 and APLP2, stimulating internalization of the bispecific antibodies, e.g., under circumstances where degradation and lysosomal trafficking of HER2 or the antibodies is beneficial or desirable. For example, the bispecific antibodies can direct bispecific anti-HER2xAPLP2 antibody drug conjugates (ADCs) into the lysosomes of specific HER2-expressing cells, such as breast tumor cells, for release of the drug conjugate and targeted cytotoxicity. The present invention also provides antibodies and antigen-binding fragments thereof that bind to human HER2. The antibodies according to this aspect of the invention are useful, inter alia, for targeting cells expressing HER2. The present invention also provides antibodies and antigen-binding fragments thereof that bind to human APLP2. The antibodies according to this aspect of the invention are useful, inter alia, for targeting cells expressing APLP2 and a target antigen, such as HER2, for rapid internalization of the binding molecule into the cell by APLP2.

[0008] Exemplary anti-HER2 antibodies of the present invention are listed in Table 1. Table 1 sets forth the amino acid and nucleic acid sequence identifiers of the heavy chain variable regions (HCVRs) and light chain variable regions (LCVRs), as well as heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3), and light chain complementarity determining regions (LCDR1, LCDR2 and LCDR3) of the exemplary anti-HER2 antibodies.

[0009] The present invention provides antibodies, or antigen-binding fragments thereof, comprising an HCVR comprising an amino acid sequence selected from any of the HCVR amino acid sequences listed in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0010] The present invention also provides antibodies, or antigen-binding fragments thereof, comprising an LCVR comprising an amino acid sequence selected from any of the LCVR amino acid sequences listed in Table 1, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity thereto.

[0011] The present invention also provides antibodies, or antigen-binding fragments thereof, comprising an HCVR and an LCVR amino acid sequence pair (HCVR/LCVR) comprising any of the HCVR amino acid sequences listed in Table 1 paired with any of the LCVR amino acid sequences listed in Table 1. According to certain embodiments, the present invention provides antibodies, or antigen-binding fragments thereof, comprising an HCVR/LCVR amino acid sequence pair contained within any of the exemplary anti-